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Inventor: Hiroko YANAGA
EXHIBIT A

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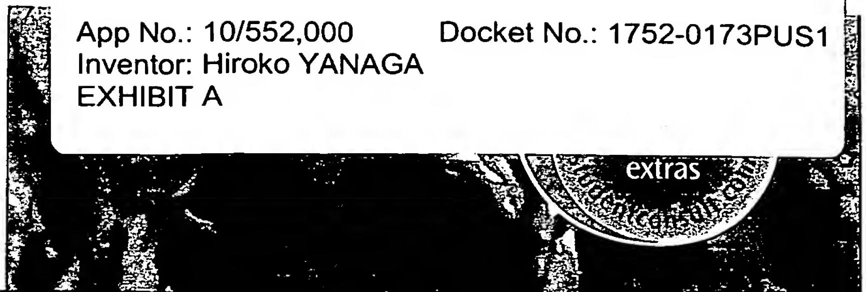
James L. Hiatt



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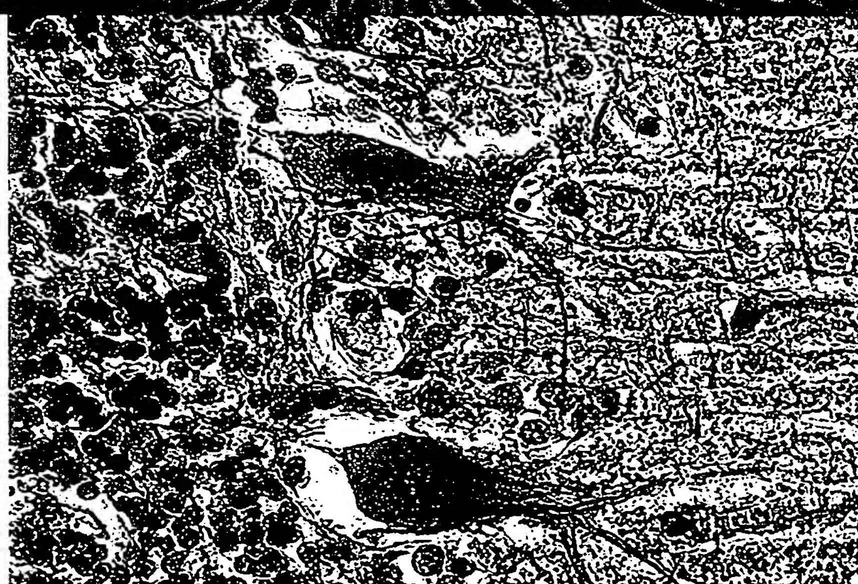

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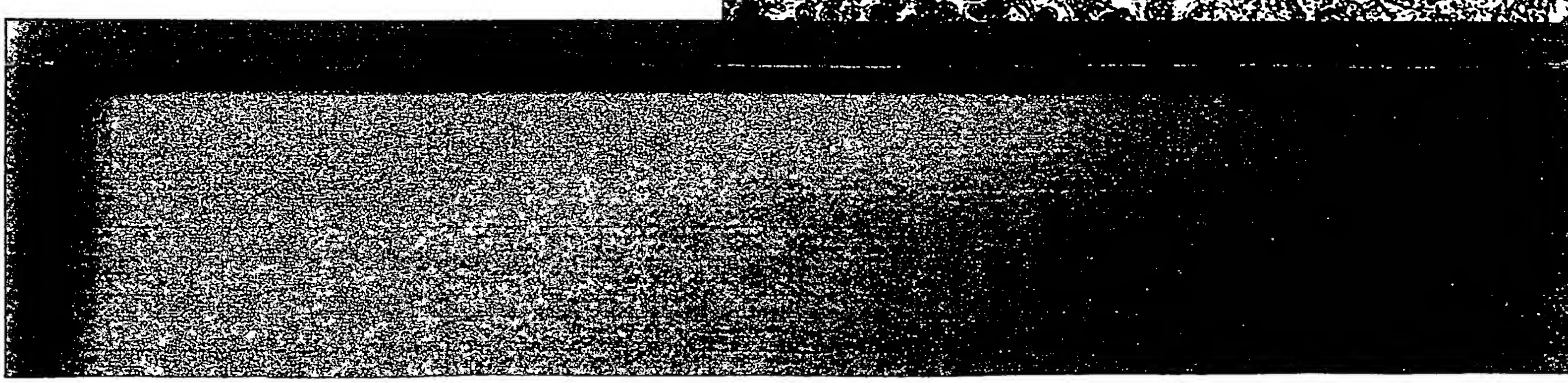

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7

Cartilage and Bone

Cartilage and bone are both specialized connective tissues. Cartilage possesses a firm pliable matrix that resists mechanical stresses. Bone matrix is one of the hardest tissues of the body, and it too resists stresses placed upon it. Both of these connective tissues have cells that are specialized to secrete the matrix in which, subsequently, the cells become trapped. Although cartilage and bone have many varied functions, some of the functions are similar and related. Both are involved in supporting the body because they are intimately associated in the skeletal system. Most of the long bones of the body are formed first in the embryo as cartilage, which then acts as a template that is later replaced by bone; this process is referred to as **endochondral bone formation.** Most of the flat bones are formed within preexisting membranous sheaths; thus this method of osteogenesis is known as **intramembranous bone formation.**

CARTILAGE

Cartilage possesses cells called **chondrocytes,** which occupy small cavities called **lacunae** within the **extracellular matrix** they secreted. The substance of cartilage is neither vascularized nor supplied with nerves or lymphatic vessels; however, the cells receive their nourishment from blood vessels of surrounding connective tissues by diffusion through the matrix. The extracellular matrix is composed of **glycosaminoglycans** and **proteoglycans,** which are intimately associated with the collagen and elastic fibers embedded within the matrix. The flexibility and resistance of cartilage to compression permit it to function as a shock absorber, and its smooth surface permits almost friction-free movement of the joints of the body as it covers the articulating surfaces of the bones.

There are three types of cartilage according to the fibers present in the matrix (Fig. 7-1 and Table 7-1):

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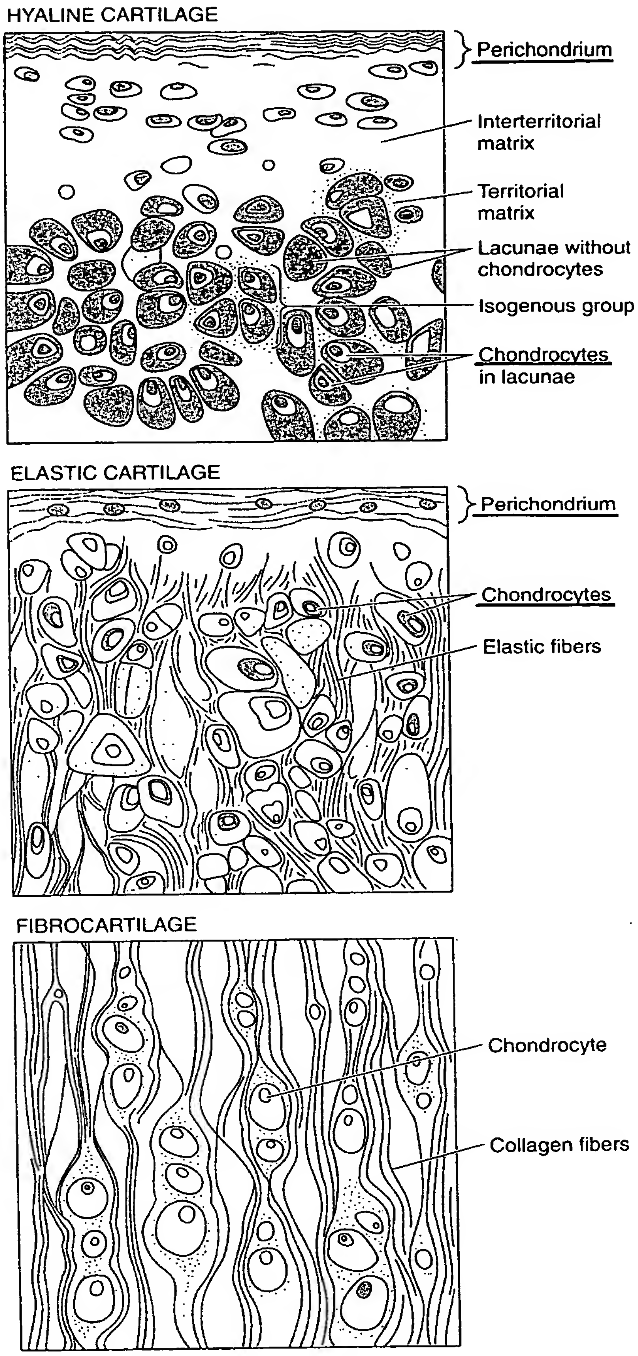
The **perichondrium** is a connective tissue sheath covering that overlies most cartilage. It has an outer fibrous layer and inner cellular layer whose cells secrete cartilage matrix. The perichondrium is vascular, and its vessels supply nutrients to the cells of cartilage. In areas where the cartilage has no perichondrium (e.g., the articular surfaces of the bones forming a joint), the cartilage cells receive their nourishment from the synovial fluid that bathes the joint surfaces. Perichondria are present in elastic and most hyaline cartilages, but absent in fibrocartilage.

Hyaline Cartilage

Hyaline cartilage, the most abundant cartilage in the body, forms the template for endochondral bone formation.

Hyaline cartilage, a bluish-gray, semitranslucent, pliable substance, is the most common cartilage of the body. It is located in the nose and larynx, on the ventral ends of the ribs where they articulate with the sternum, in the tracheal rings and bronchi, and on the articulating surfaces of the movable joints of the body. Also, it is this cartilage that forms the cartilage template of many of the bones during embryonic development and constitutes the epiphyseal plates of growing bones (see Table 7-1).



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Histogenesis and Growth of Hyaline Cartilage

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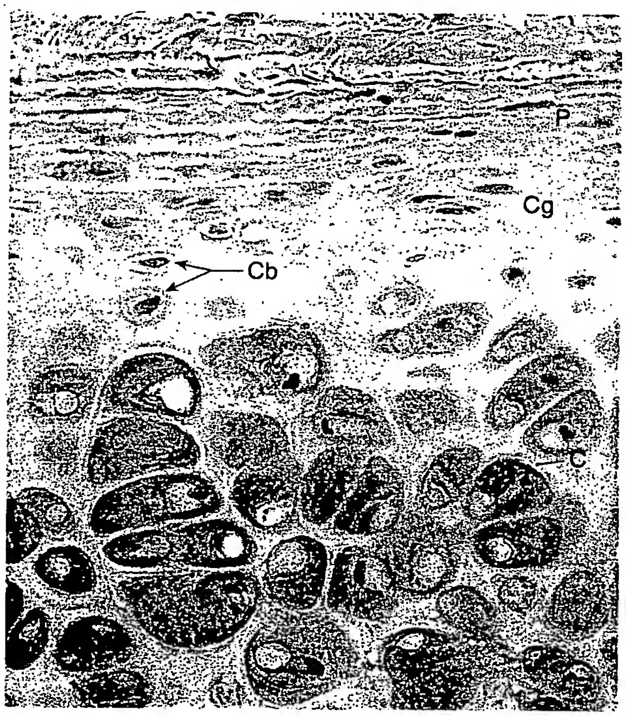

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The matrix of hyaline cartilage contains primarily **type II collagen,** but types IX, X, and XI and other minor collagens are also present in small quantities. Type II collagen does not form large bundles, although the bundle thickness increases with distance from the lacunae. Fiber orientation appears to be related to the stresses placed on the cartilage. For example, in articular cartilage, the fibers near the surface are oriented parallel to the surface, whereas deeper fibers seem to be oriented in curved columns.

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A small region of the matrix, 1- to 3-mm thick, immediately surrounding the lacuna is known as the **pericellular capsule.** It displays a fine meshwork of collagen fibers embedded in a basal lamina-like substance. These fibers may represent some of the other minor collagens present in hyaline cartilage; it has been suggested that the pericellular capsule may protect chondrocytes from mechanical stresses.

Cartilage matrix is rich in **aggrecans,** large proteoglycan molecules composed of protein cores to which glycosaminoglycan molecules (chondroitin 4-sulfate, chondroitin 6-sulfate, and heparan sulfate) are covalently linked (see Fig. 4-3). As many as 100 to 200 aggrecan molecules are linked noncovalently to hyaluronic acid, forming huge aggrecan composites that can be 3- to 4-μm long. The abundant negative charges associated with these exceedingly large proteoglycan molecules attract cations, predominantly Na^+ ions, which in turn attract water molecules. In this way, the cartilage matrix becomes hydrated to such an extent that up to 80% of the wet weight of cartilage is water, accounting for the ability of cartilage to resist forces of compression.

Not only do hydrated proteoglycans fill the interstices among the collagen fiber bundles, but their glycosaminoglycan side chains form electrostatic bonds with the collagen. Thus, the ground substance and fibers of the matrix form a cross-linked molecular framework that resists tensile forces.

Cartilage matrix also contains the adhesive glycoprotein **chondronectin.** This large molecule, similar to fibronectin, has binding sites for type II collagen, chondroitin 4-sulfate, chondroitin 6-sulfate, hyaluronic acid, and integrins (transmembrane proteins) of chondroblasts and chondrocytes. Chondronectin thus assists these cells in maintaining their contact with the fibrous and amorphous components of the matrix.

Histophysiology of Hyaline Cartilage

The smoothness of hyaline cartilage and its ability to resist forces of both compression and tension are essential to its function at the articular surfaces of joints. Because cartilage is avascular, nutrients and oxygen must diffuse through the water of hydration present in the matrix. The inefficiency of such a system necessitates a limit on the width of cartilage. There is a constant turnover in the proteoglycans of cartilage that changes with age. Hormones and vitamins also exert influence on the growth, development, and function of cartilage. Many of these substances also affect skeletal formation and growth (Table 7-2).

CLINICAL CORRELATIONS

Hyaline cartilage degenerates when the chondrocytes hypertrophy and die and the matrix begins to calcify. This process is a normal and integral part of endochondral bone formation; however, it is also a natural process of aging, often resulting in less mobility and in joint pain.

Cartilage regeneration is usually poor except in children. Chondrogenic cells from the perichondrium enter the defect and form new cartilage. If the defect is large, the cells form dense connective tissue to repair the scar.

Elastic Cartilage

Elastic cartilage greatly resembles hyaline cartilage, except that its matrix and perichondrium possess elastic fibers.

Elastic cartilage is located in the pinna of the ear, the external and internal auditory tubes, the epiglottis, and

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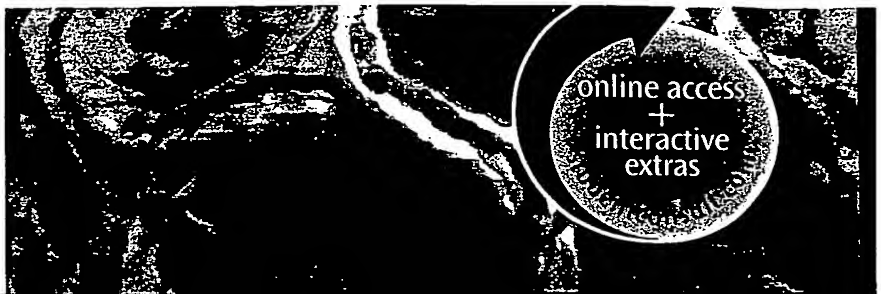

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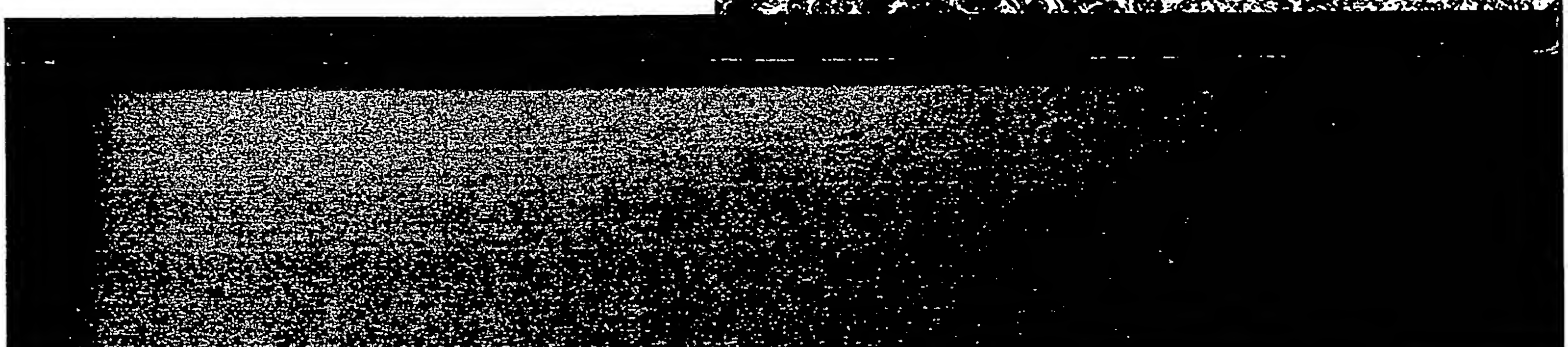

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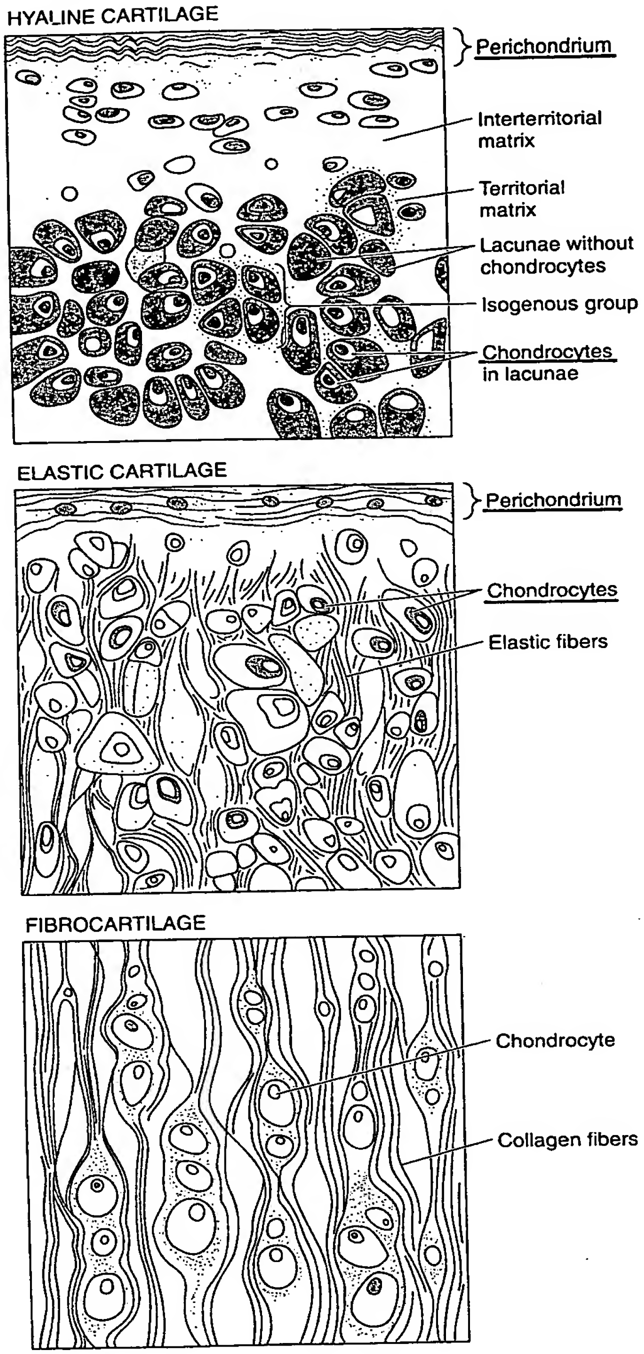

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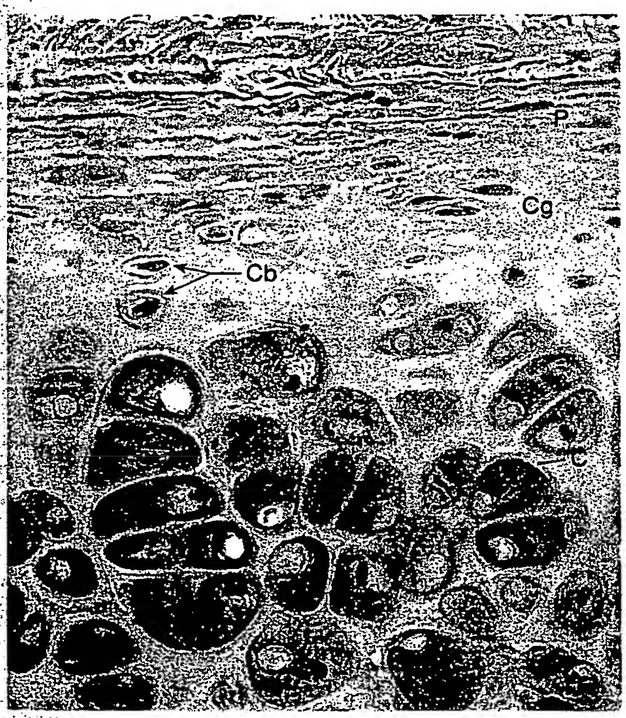

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The smoothness of hyaline cartilage and its ability to resist forces of both compression and tension are essential to its function at the articular surfaces of joints. Because cartilage is avascular, nutrients and oxygen must diffuse through the water of hydration present in the matrix. The inefficiency of such a system necessitates a limit on the width of cartilage. There is a constant turnover in the proteoglycans of cartilage that changes with age. Hormones and vitamins also exert influence on the growth, development, and function of cartilage. Many of these substances also affect skeletal formation and growth (Table 7-2).

CLINICAL CORRELATIONS

Hyaline cartilage degenerates when the chondrocytes hypertrophy and die and the matrix begins to calcify. This process is a normal and integral part of endochondral bone formation; however, it is also a natural process of aging, often resulting in less mobility and in joint pain.

Cartilage regeneration is usually poor except in children. Chondrogenic cells from the perichondrium enter the defect and form new cartilage. If the defect is large, the cells form dense connective tissue to repair the scar.

Elastic Cartilage

Elastic cartilage greatly resembles hyaline cartilage, except that its matrix and perichondrium possess elastic fibers.

Elastic cartilage is located in the pinna of the ear, the external and internal auditory tubes, the epiglottis, and